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Palivizumab Dosing And Risk Of Rsv Infection In Premature Children

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Abstract

We conducted a retrospective case-control study of children attending the Yale-New Haven Hospital Premature Infant Primary Care Clinic (YNHH-PIPCC). Subjects were prematurely born children under 24 months of age cared for at the YNHH-PIPCC between October 2000 and March 2011. They are eligible to receive monthly passive respiratory syncytial virus (RSV) immunization with palivizumab during the RSV season. All cases had laboratory-documented severe RSV disease necessitating hospital admission or outpatient visit. Controls did not have severe RSV disease during the same season as their matched case. Controls were matched to the cases by gestational age and month of birth. Risk of severe RSV disease was estimated using matched ORs and adjusted for potential confounders with the use of conditional logistic regression. The hypothesis of this study is that receiving less than all expected doses of palivizumab reduces the effectiveness of palivizumab in preventing severe RSV disease. Of 299 eligible subjects identified during the study's 11 RSV seasons (October 2000 through March 2011), 28 (9%) experienced RSV infections. Of the 28 subjects with RSV infection, 24 (85.7%) subjects were adherent to the dosing protocol. Severe RSV disease requiring hospital admission was noted in 15 of 217 (7%) of adherent subjects compared with 3 of 72 (4%) of non-adherent subjects. Cases of severe RSV disease were more likely to be Hispanic (61% vs. 39%; p-value: 0.05) than matched controls. There was no association between adherence to the dosing protocol and hospital admission due to severe RSV disease. These findings suggest the need for further study of palivizumab dosing recommendations and factors that may be influencing adverse health events in premature Hispanic children receiving health care at the YNHH-PIPCC.

Introduction

Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract morbidity, especially bronchiolitis and pneumonia in children under two years of age. In the United States, approximately 75,000—125,000 RSV-related infant hospitalizations occur annually [1]. Annual epidemics of RSV infection occur over a 5-month season from November through March in temperate climates. Seasonality is a significant factor in determining the risk of infection. Although RSV infects people of all ages, children under two years of age are particularly susceptible. Risk factors of severe RSV infection include preterm birth, chronic lung disease, congenital heart disease, immunodeficiency, and receipt of immunosuppressive therapy [2].

Premature infants are at high risk for severe RSV infection that often requires hospitalization. Although there is no existing active immunization for the prevention of RSV infection, passive immunization with palivizumab (Synagis), a humanized monoclonal antibody that binds the F-protein of RSV, has been shown to reduce the risk of RSV hospitalization from 39% to 78% among high-risk infants, depending on the subsets of the study sample [3]. There was a 39% reduction in RSV hospitalization in premature infants with bronchopulmonary dysplasia and a 78% reduction in premature infants with no bronchopulmonary dysplasia. A monthly injection of palivizumab is recommended to protect high-risk infants throughout the months of each RSV season [4]. The price of a full 5-dose regimen can exceed $8000 (average wholesale price), depending on the recipient's body weight [5]. Due to its cost, palivizumab is limited in its administration to populations at the highest risk for severe RSV illness.

Monthly doses of palivizumab are recommended to maintain a threshold serum

concentration of anti-RSV antibody, the rationale for which is based largely on previous studies of palivizumab [3]. These have examined cost-effectiveness of palivizumab prophylaxis, adherence to monthly palivizumab prophylactic guidelines, and the efficacy of compliance at reducing RSV infection-related hospitalization in high-risk infants [3, 6-9]. Little data is available, however, on quantifying the risk of RSV disease in high-risk patients when they miss monthly doses of palivizumab.

The proposed study aims to evaluate whether incomplete monthly palivizumab dosing regimens lead to decreased protection from severe RSV disease (i.e. RSV infection necessitating hospitalization or a hospital outpatient visit) compared with complete dosing regimens. An incomplete dosing regimen in a premature infant is defined as one where an infant did not receive all expected palivizumab doses at the time of a scheduled monthly outpatient visit to the Yale-New Haven Hospital Premature Infant Primary Care Clinic (YNHH-PIPCC).

Previous studies in premature infants have shown that a complete palivizumab course offers a reduced risk of hospitalization due to RSV infection of 55% [3], whereas an incomplete regimen was associated with a significantly higher proportion of hospitalizations [9]. Accordingly, the hypothesis of this study is an incomplete palivizumab regimen due to missed doses reduces the effectiveness of palivizumab in preventing hospitalization due to RSV infection. Such a finding could warrant a re-evaluation of the efficiency and cost-effectiveness of current palivizumab dosing recommendations in high-risk premature infants.

Methods

Enrollment

We conducted a retrospective case-control medical record review of premature infants attending the YNHH-PIPCC. Study subjects were premature children who were cared for at the YNHH-PIPCC between October 2000 and March 2011 and who were eligible to receive palivizumab according to Pediatric Red Book guidelines.

Study subjects were identified from YNHH-PIPCC database, which contained names, medical record numbers, and birth dates for all palivizumab eligible patients from October 2000 through March 2011, a total of eleven RSV seasons.

Case subjects were children under 24 months of age cared for at the YNHH-PIPCC who were palivizumab eligible (according to Pediatric Red Book guidelines) and were admitted to the hospital as an inpatient or as an Emergency Department visit due to RSV infection during the 2000 to 2011 RSV seasons.

Control subjects were children less than 24 months of age cared for at the YNHH-PIPCC who were palivizumab eligible (according to Pediatric Red Book guidelines), but who did not have RSV disease during the same season as their matched case. Controls were matched to cases by gestational age (±2 weeks from the gestational age of the case) and season of birth (±1 month of the birth month of the case). The controls were matched to cases systematically so that preference was given to controls that were within one week of gestational age of the case.

Data Collection

Clinical and demographic data for study subjects were obtained from YNHH's electronic medical record systems Sunrise Clinical Manager and Logician, including laboratory data on RSV results from specimens submitted to the clinical virology laboratory.

Demographic and clinical data included date of birth, race, gender, gestational age, birth weight, intubation at birth, hospital length of stay after birth, underlying conditions (congenital heart disease, chronic lung disease, HIV), palivizumab administration dates, RSV infection dates, and hospital length of stay for RSV infection. Study personnel created a standardized medical record review form to abstract data from each subject's medical record. All information was then entered into Microsoft Access 2007.

According to the American Academy of Pediatrics' Red Book (2009), indications for palivizumab eligibility specify that a maximum of 5 monthly doses may be administered to children younger than 24 months of age with congenital heart disease, chronic lung disease of prematurity, or a preterm birth at less than 32 weeks gestation. The protocol recommends that strict adherence to monthly administration be maintained.

Adherence, based strictly on the dosing recommendations, was defined as follows: Depending on the month of birth, the child received all expected doses and did not miss a monthly dose. For example, if the first dose was given in December, then it was expected that the child received four doses through March. Subjects not receiving a full palivizumab course were categorized as non-adherent. Cases and controls were stratified by adherence according to whether they received complete dose regimens (received all

expected doses) or incomplete dose regimens (did not received all expected doses).

Data Analysis

The number of doses of palivizumab received by cases and controls was assessed through medical record review. Data for palivizumab was stratified by number of doses received, distinguishing between those who received a complete dose regimen—the infant received a monthly dose throughout the RSV season—or an incomplete dose regimen—the infant failed to receive one or more expected monthly doses during the RSV season. Bivariate analysis using a χ^2 test of association was used to examine associations between subject characteristics and RSV disease status. The risk of severe RSV disease was estimated directly from matched odds ratios. Conditional logistic regression was used to adjust for potential confounders. Matched odds ratios measuring the association of risk factors and RSV infection were calculated with logistic regression in SAS version 9.2. Tests were conducted at the α level of 0.05 for statistical significance. P-values equal to or less than 0.05 were considered significant.

Ethical Approval

All study procedures were approved by the Human Investigation Committee at Yale University.

Results

A total of 299 study eligible subjects were identified between October 2000 and March 2011. Overall, 28 (9.4%) RSV infections were identified during the 11 RSV seasons. Infections occurred during months of October through April, with a majority of the infections occurring from December through February (Figure 1).

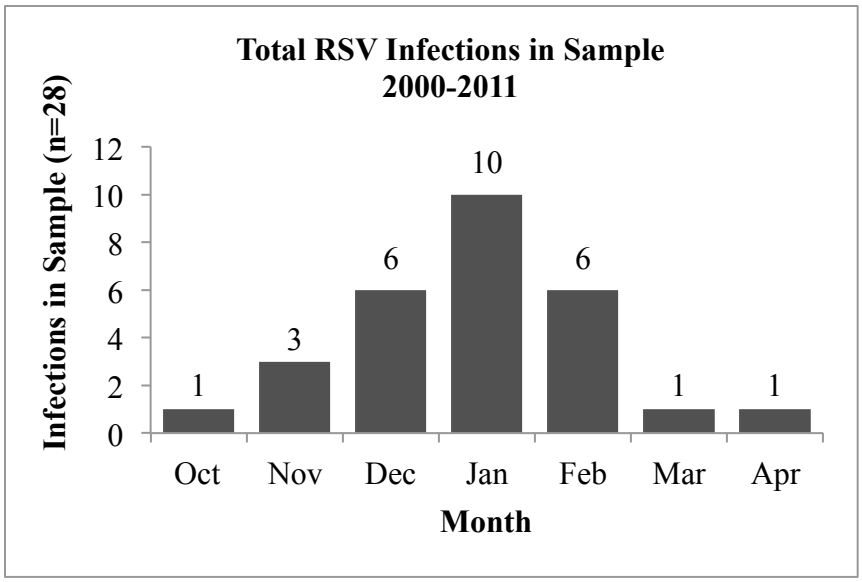

Figure 1. RSV infections by month from October 2000 - March 2011 in the study sample.

This distribution of infections follows the typical pattern of RSV infection in temperate climates as defined in CDC surveillance reports. Of the 28 infections, 18 (64%) resulted in hospitalization and 10 (36%) ED visits or clinic visits. Subject characteristics are shown in Table 1. The majority of children were Black (59.9%) or Hispanic (32.8%). Overall, 95% had received at least one dose of palivizumab and 226 (75.6%) were found to be adherent to the dosing protocol. Of the 28 subjects with RSV infection, 24 (85.7%) subjects were adherent to the dosing protocol. Severe RSV disease requiring hospital admission was noted in 15 of 217 (7%) of adherent subjects compared with 3 of 72 (4%)

of non-adherent subjects. This difference was not statistically different (p-value: 0.19). Ethnicity and congenital heart disease were the only characterizing variables that were statistically significant in explaining an association with RSV infection (Table 1).

Table 1. Summary of characteristics of the study population by RSV infection.

Characteristic	**RSV+ n = 28 (%)**	**RSV- n = 271 (%)**	**p**
Race/ethnicity			0.02
White	0 (0)	16 (6)	
Black	13 (46)	166 (61)	
Hispanic	13 (46)	85 (31)	
Asian	1 (4)	0 (0)	
Other	1 (4)	4 (2)	
Sex			0.58
Male	16 (57)	140 (52)	
Female	12 (43)	131 (48)	
Mechanical Intubation			0.14
Yes	4 (14)	18 (7)	
No	24 (86)	253 (93)	
Chronic Lung Disease†			0.47
Yes	13 (46)	107 (39)	
No	15 (54)	164 (61)	
Congenital Heart Disease			0.01
Yes	8 (29)	32 (12)	
No	20 (71)	239 (88)	
Non-adherent to dosing protocol*			0.19
Yes	4 (14)	69 (25)	
No	24 (86)	202 (75)	

ϕIncluded: Hemodynamically significant cyanotic or acyanotic congenital heart disease, atrial septal defect, ventricular septal defect, peripheral pulmonary stenosis, patent ductus arteriosus.
*****Definition of adherence: Depending on the month of birth, the child received all expected doses and did not miss a monthly dose.

To assess if there were any predictors of non-adherence, non-adherent subjects were compared with subject characteristics (Table 2). There were no differences in adherence to dosing for any subject characteristics.

Table 2. Associations between subject characteristics and nonadherent subjects.

Characteristic	**Cases n = 18**	**Controls n = 271**	**N**	**Nonadherent* N (%)**	**p**
Race/ethnicity					0.52
White	0	16	16	5 (31)	
Black	6	166	172	45 (26)	
Hispanic	11	85	96	22 (23)	
Asian	0	0	1	0	
Other	1	4	5	0	
Sex					0.42
Male	8	131	139	42 (30)	
Female	10	140	150	30 (20)	
Mechanical Intubation					0.35
Yes	4	18	22	7 (32)	
No	14	253	267	65 (24)	
Chronic Lung Disease					0.40
Yes	8	107	115	29 (25)	
No	10	164	174	43 (25)	
Congenital Heart Disease$^{\phi}$					0.52
Yes	6	32	38	6 (16)	
No	12	239	251	66 (26)	

$^{\phi}$Included: Hemodynamically significant cyanotic or acyanotic congenital heart disease, atrial septal defect, ventricular septal defect, peripheral pulmonary stenosis, patent ductus arteriosus.
*****Definition of adherence: Depending on the month of birth, the child received all expected doses and did not miss a monthly dose.

Characteristics of cases and controls are shown in Table 3. Of the 299 subjects, a total of 289 were eligible for the matched analysis. The ten ineligible controls did not meet matching criteria for gestational age (±2 weeks from the gestational age of the case) and seasonality of birth (±1 month of the birth month of the case). Cases of RSV were more likely to be Hispanic (61% vs. 39%; p-value: 0.05) than their matched controls. We examined the risk of RSV hospitalization for all other race combinations, but did not find any significant predictors of cases based on these other race combinations.

Table 3. Characteristics of cases and controls.

Characteristic	**Cases n = 18 (%)**	**Controls n = 271 (%)**	**Matched OR (95% CI)**	**p**
Race/ethnicity				
All other races	7 (39)	186 (69)	Reference	
Hispanic	11 (61)	85 (31)	3.46 (1.02, 11.80)	0.05
Sex				
Female	8 (56)	131 (48)	Reference	
Male	10 (44)	140 (52)	1.10 (0.41, 2.91)	0.85
Mechanical Intubation				
No	14 (78)	253 (93)	Reference	
Yes	4 (22)	18 (7)	3.43 (0.67, 17.69)	0.14
Chronic Lung Disease				
No	10 (56)	164 (61)	Reference	
Yes	8 (44)	107 (39)	1.40 (0.37, 5.25)	0.61
Congenital Heart Disease$^{\phi}$				
No	12 (67)	239 (88)	Reference	
Yes	6 (33)	32 (12)	3.71 (0.95, 14.39)	0.06
Non-adherent to dosing protocol*				
No	15 (83)	202 (75)	Reference	
Yes	3 (17)	69 (25)	0.92 (0.21, 4.08)	0.91

$^{\phi}$Included: Hemodynamically significant cyanotic or acyanotic congenital heart disease, atrial septal defect, ventricular septal defect, peripheral pulmonary stenosis, patent ductus arteriosus.
*Definition of adherence: Depending on the month of birth, the child received all expected doses and did not miss a monthly dose.

Matched odds ratios of the association between ethnicity and non-adherence with hospitalization due to RSV infection are shown in Table 4. When we controlled for potential confounders, Hispanic subjects continued to be at increased risk of hospitalization when compared with all other races (OR: 3.47; 95% CI: 1.01-11.84; p - value: 0.05). However, we did not find an association between adherence to the dosing protocol, defined as receiving all expected doses during an RSV season, and hospitalization due to RSV infection. Non-adherent subjects were no more likely than adherent subjects to be cases.

Table 4. Multivariate logistic regression model of characteristics associated with hospitalization due to respiratory syncytial virus infection (N = 289).

Characteristic	**Cases n = 18 (%)**	**Controls n = 271 (%)**	**Matched OR (95% CI)**	**p**
Race/ethnicity				
All other races	7 (39)	186 (69)	Reference	---
Hispanic	11 (61)	85 (31)	3.47 (1.01, 11.84)	0.05
Non-adherent to dosing protocol*				
No	15 (83)	202 (75)	Reference	---
Yes	3 (17)	69 (25)	1.02 (0.23, 4.50)	0.98

*Definition of adherence: Depending on the month of birth, the child received all expected doses and did not miss a monthly dose.

In the bivariate analysis, the test association between Hispanic ethnicity and study characteristics identified two statistically significant associations. First, being Hispanic was associated with having congenital heart disease (p-value: 0.03). Additionally, being Hispanic was associated with hospitalization due to RSV infection (p-value: 0.01).

Discussion

This case-control study examines the risk of severe RSV disease due to a failure in receiving all expected palivizumab doses during an RSV season. Non-adherence to the recommended dosing protocol, defined as failing to receive all expected doses throughout an RSV season, was found to have no association with hospitalization due to RSV infection. Hispanic children were found to be at increased risk for hospitalization due to RSV infection (OR: 3.47, 95% CI: 1.01-11.84) when controlling for potential confounders. Based on these results, efforts to maintain complete adherence to the dosing protocol may not be necessary. Missing one of the expected doses during the RSV season may not put a child at increased risk of RSV hospitalization. Optimal palivizumab dosing for the prevention of RSV infection must take into account the increased risk of severe RSV disease in Hispanic children.

The lack of a significant association between missing one or more doses of palivizumab and being hospitalized due to RSV infection may be partially explained by palivizumab titer in children who received the drug. Monthly doses of palivizumab are recommended to maintain a threshold serum concentration of anti-RSV antibody. The target for threshold serum concentration is 40 μg/ml, which was derived from preclinical data in rats. Rats maintaining levels greater than this threshold showed a 99% reduction in pulmonary RSV. The IMpact RSV-Group reported data on serum concentration of palivizumab in premature infants as part of the palivizumab approval study [3]. The data suggest the trend of a cumulative effect of serum concentration through monthly dosing at 15mg/kg concentration. If a child missed one dose but maintained a serum concentration level above the threshold level of anti-RSV antibody, then the child may

still be protected against viral insult. Another possibility is that children who were adherent were at higher risk for severe disease than children who were non-adherent due to factors that were not detected in our analysis.

An interesting finding in the current study was that Hispanic children were more likely to have congenital heart disease and more likely to be hospitalized with severe RSV disease when compared with all other ethnicities. Although congenital heart disease was not found to be associated with RSV hospitalization, the increased risk of congenital heart disease in Hispanics may be a factor in explaining the high proportion of RSV hospitalization among this group of children.

This study was not without limitations. Subjects were enrolled from a single healthcare center, so there was a relatively small sample size with only 28 subjects infected with RSV and 18 hospitalizations due to RSV in 11 seasons. However, study personnel were able to capture all eligible children who attended the YNHH-PIPCC. Additionally, data on palivizumab administration for children at YNHH was thoroughly recorded from the first RSV season that the drug was administered. YNHH-PIPCC consistently administered palivizumab, as can be seen in the high proportion (75%) of children receiving a full course of the prophylactic drug. This may partially explain the low number of RSV infections in the sample.

Palivizumab was developed to prevent RSV infection, not necessarily to prevent RSV hospitalization. The reported results restricted the analysis to children hospitalized with RSV disease (n=18). However, including all 28 RSV-infected children in the analysis did not significantly change results. Limiting cases to children hospitalized with RSV infection was necessary to capture only severe RSV infections. Because children

may have acquired RSV infection without seeking or acquiring medical care, estimated associations between RSV infection and characteristics of subjects would have been biased had we not separated the most severe RSV cases from the controls.

The findings of this study prompt a continued investigation of the effectiveness of palivizumab dosing recommendations. Capturing more cases by expansion to additional study sites is necessary to improve precision in identifying associations between subject characteristics and clinical outcomes. With these additional data, palivizumab-eligible children can be stratified based on every dose received. The effectiveness of each dose can be directly estimated. Furthermore, a greater distribution of the ethnicities enrolled in this study would be beneficial for comparing risk factors for severe RSV disease. To examine if palivizumab titer influences the risk of RSV infection, a laboratory component could be designed to measure serum concentrations for infants receiving palivizumab. This information could be related to the risk of RSV infection among adherent and non-adherent dosing groups receiving various numbers of doses throughout an RSV season.

Preterm children are at increased risk of respiratory syncytial virus infection. This retrospective study shows palivizumab dosing adherence over 11 RSV seasons at the Yale-New Haven Hospital Premature Infant Primary Care Clinic and relates it to the risk of hospitalization due to RSV. No association was found between RSV hospitalization and dosing adherence. However, Hispanic children were found to be at increased risk of RSV hospitalization and congenital heart disease. This finding should prompt further exploration of factors that may be influencing adverse health events in Hispanic preterm infants receiving health care at the Yale-New Haven Hospital Premature Infant Primary Care Clinic.

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